Efficient *mono*- and *bis*-functionalization of 3,6-dichloropyridazine using $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$†

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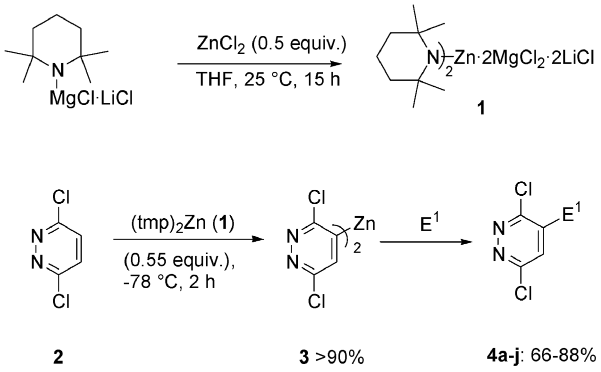
3,6-Dichloropyridazine undergoes a smooth metallation using $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$. The resulting *bis*-organozinc species react with various electrophiles; subsequent functionalization *via* a second metallation proceeds readily; further reactions with hydrazine lead to highly substituted pyrazolo[3,4-*c*]pyridazines derivatives.

The directed metallation of aromatics and heteroaromatics is one of the important tools to functionalize these scaffolds.[1] Especially, the metallation of nitrogen-containing heterocycles is of great interest.[2] Using LiTMP or related methods, the metallation and successive reactions with electrophiles often lead to low yields due to the instability of lithiated heterocycles.[3] Recently, we have reported the preparation of the neutral mixed-metal complex base $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**).[4] This base combines high reactivity with excellent functional groups tolerance. Sensitive heterocycles which are prone to undergo ring-opening like [1,3,4]-oxadiazole[5] can be smoothly zincated using **1** (0.55 equiv.) at 25 °C and further functionalized. The base $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**) is easily prepared by the reaction of tmpMgCl·LiCl[6] with $ZnCl_2$ (Scheme 1). Herein, we wish to report the efficient functionalization of 3,6-dichloropyridazine (**2**) which is an important substrate for the preparation of polyfunctional pyridazine derivatives.[3a,7]

Thus, the reaction of 3,6-dichloropyridazine (**2**) with **1** gives the zincated intermediate **3** in over 90% yield within 2 h at –78 °C (Scheme 1). This new zinc reagent **3** can be reacted with various electrophiles (see Table 1).

Therefore, the reaction of the zinc reagent **3** with iodine afforded the iodinated 3,6-dichloropyridazine **4a** in 82% yield (Table 1, entry 1). Conventional methods provided this product in 32% yield.[3a] The reaction with ethyl 2-(bromomethyl)-acrylate[8] in the presence of CuCN·2LiCl[9] (25 mol%) furnished the allylated product **4b** in 85% yield (entry 2). Furthermore, the zincated pyridazine derivate **3** can also be transmetallated with CuCN·2LiCl[8] to promote the reaction with acid chlorides. The subsequent addition of various acid chlorides led to the ketones **4c–4e** in 66–73% yield within 16 h at –20 °C (entries 3–5). Moreover, after the addition of chloranil (0.6 equiv.)[10] to **3**, the dimeric pyridazine **4f** was obtained in 88% yield (entry 6).



Scheme 1

Remarkably, low-temperature Pd-catalyzed cross-coupling reactions[11] can also be performed using $Pd(dba)_2$ (5 mol%) and P(*o*-furyl)$_3$ (10 mol%) as a catalyst system with simultaneous warming of the reaction mixture from –78 °C to –20 °C within 4 h. Electron-poor as well as electron-rich electrophiles are leading to the functionalized biaryls **4g–i** in 76–81% yield (entries 7–9).

Various substituted 3,6-dichloropyridazine can be further functionalized using $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**) leading to the new zincated pyridazine of type **5** within 3 h at –78 °C (Scheme 2).

Therefore, the iodolysis of the metallated 3,6-dichloro,-4-iodopyridazine (**4a**) gave the diiodide **6a** in 56% yield (entry 10). The zincation of **4c** with subsequent reaction with benzoyl chloride in the presence of CuCN·2LiCl[8] provided the symmetrical *bis*-ketosubstituted pyridazine **6b** in 77% yield (entry 11). The ketone **4d** can also be further functionalized by the reaction with ethyl 2-(bromomethyl)acrylate[8] in the presence of CuCN·2LiCl (25 mol%)[9] giving the substituted pyridazine derivative **6c** in 75% yield (entry 12).

The ketones **4c** and **4d** can also be converted into the annelated heterocyclic system of type **7** using hydrazine-hydrate as ring-closing agent[12] within 15 min giving the corresponding pyrazolo[3,4-*c*]pyridazines **7a** and **7b** in 66–75% yield (Scheme 2). Additionally, the related thiopheno[2,3-*c*]-pyridazines **7a** and **7b** have been prepared by the reaction of **4c** and **4d** with $HSCH_2CO_2Me$ in the presence of NEt_3.[13] After 6 h in refluxing MeOH the annelated compounds **8a** and **8b** could be isolated in 79–85% yield (Scheme 3).

In summary, we have reported a highly efficient functionalization of 3,6-dichloropyridazine (**2**) with $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**). The smooth metallations are carried out at –78 °C and lead to various substituted pyridazines which are of high interest for their potential pharmaceutical properties.[14]

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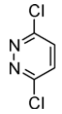
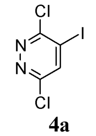
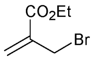
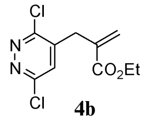
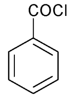
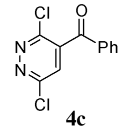
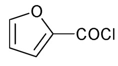
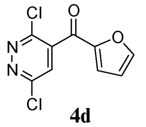
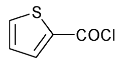
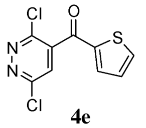
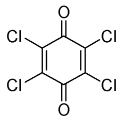
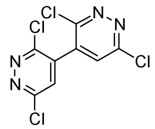
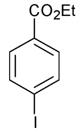
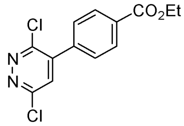
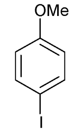
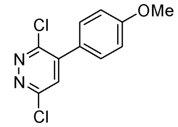
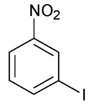
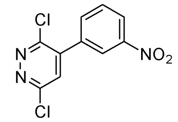
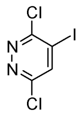
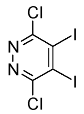
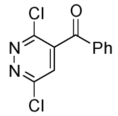
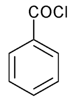
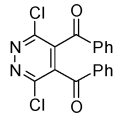
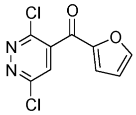
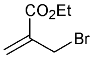
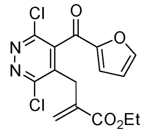
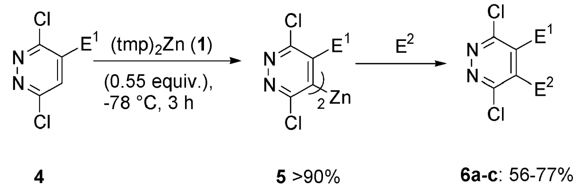
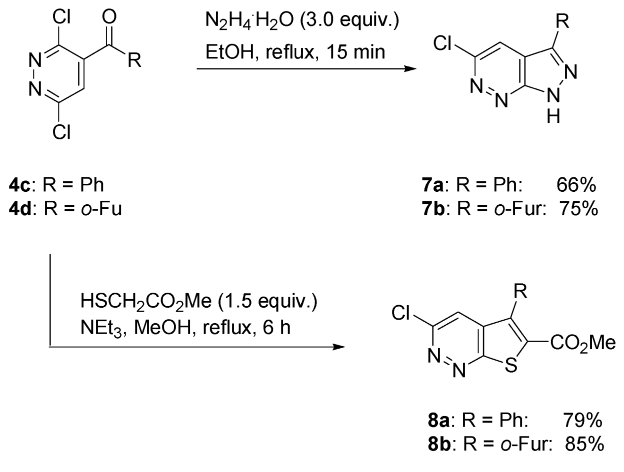
Table 1 Products of type **4** and **5** obtained by *mono* or *bis*-zincation of **2** using $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1) and subsequent reactions with electrophiles

Entry	Substrate	Electrophile	Product	Yield[a] (%)
1	 **2**	I_2	 **4a**	82
2	**2**		 **4b**	85[b]
3	**2**		 **4c**	73[c]
4	**2**		 **4d**	68[c]
5	**2**		 **4e**	66[c]
6	**2**		 **4f**	88
7	**2**		 **4g**	81[d]
8	**2**		 **4h**	76[d]
9	**2**		 **4i**	77[d]
10	 **4a**	I_2	 **6a**	56
11	 **4c**		 **6b**	77[c]
12	 **4d**		 **6c**	75[b]

[a] Isolated yield of analytically pure product. [b] $CuCN{\cdot}2LiCl$ (25 mol%) was used. [c] $CuCN{\cdot}2LiCl$ (1.1 equiv.%) was used. [d] Obtained by palladium-catalyzed cross-coupling: $Pd(dba)_2$ (5 mol%) and tfp (10 mol%)



Scheme 2



Scheme 3

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